REMARKS

Status of Claims

Claims 1, and 3-15 are pending in this application. Claims 3-15 are withdrawn from consideration as being drawn to non-elected subject matter. Claim 1 has been amended to more particularly point out and distinctly claim that which the applicant regards as their invention. No new matter has been added by the amendment.

Claim Rejection under 35 U.S.C. §103

The rejection of claim 1 under 35 U.S.C. §103(a) as being unpatentable over Woo et al. (*Pharmaceutical Research*, vol. 18, no. 11, November 2001) in view of Filvaroff et al. (US 2002/0058614) is respectfully traversed.

The presently claimed invention is directed to a composite microsphere system consisting essentially of poly(D,L-lactide-co-glycolide) (PLGA), poly (acryloyl hydroxyethyl starch) (AcHES), and a pharmaceutically effective amount of a biologically active compound. The biologically active compound is selected from the group consisting of an insulin, an interferon, a luteinizing hormone-releasing hormone (LHRH) analog, a somatostatin and/or somatostatin derivative, a calicitonin, a parathyroid hormone (PTH), a bone morphogenic protein (BMP), an erythropoietin (EPO), an epidermal growth factor (EGF) and a growth hormone.

Woo et al. teaches that composite microspheres can be produced to carry bovine serum albumin and horseradish peroxidase. Woo et al. does not provide any teaching that the composite microspheres can successfully contain any other active ingredient.

Filvaroff et al. has been cited for its teaching that insulin can be carried in PLGA microspheres. The Office concludes that because it is known that insulin can be carried in PLGA microspheres, one of skill in the art would have expected that the composite microsphere taught in Woo et al. comprising PLGA and

acHES would be effective in carrying and delivering insulin. However, the Office fails to consider Filvaroff et al. for all that it teaches.

The PLGA microspheres taught by Filvaroff do not incorporate pure insulin, instead, the PLGA microspheres incorporate zinc-insulin complexes. Filvaroff et al. teaches that insulin has a half-life of about 5 minutes in the human body, and therefore a stabilized, slow-release formulation of human insulin is highly desirable (see paragraph [0410]). To solve this problem, Filvaroff et al. teaches that insulin can be formulated with zinc acetate to produce a sparingly soluble zinc-insulin complex, and this complex is believed to result in a longer-acting formulation (see paragraph [0410]).

If one of ordinary skill in the art looked to Filvaroff et al. for its teaching that insulin could be encapsulated by PLGA, the skilled person would be motivated to use the zinc-insulin complex because of the resulting stability. The skilled artisan, looking to create a successful delivery vehicle for insulin, would want to be sure that the insulin would not deteriorate in the human body before the body was able to absorb and use the protein. Therefore, the skilled person would want to take advantage of the known stability associated with zinc-insulin complexes. However, if the skilled person incorporated the zinc-insulin complex into the composite microsphere of Woo, they would not arrive at the presently claimed invention which uses pure insulin and not the zinc-insulin complex. By using the sparingly soluble zinc-insulin complex, the insulin would not form the hydrogel when mixed with the acHES, because the insulin would not be properly soluble to mix with the starch to form the gel. This hydrogel formation with acHES is an essential feature of the presently claimed composite microsphere.

One of ordinary skill in the art would not have a reasonable expectation of creating a stable insulin for delivery in the human body by using the composite system taught by Woo et al. There is no indication in Woo et al. that the acHES acts to stabilize the proteins themselves. Instead, Woo et al. teaches that the acHES is used to protect the proteins from contacting the harsh solvents needed

to encapsulate the protein into PLGA. The target proteins in Woo et al. were first encapsulated with an aqueous solution of hydroxyethylated starch, and those capsules were then encapsulated by PLGA. Without using hindsight reconstruction, one of ordinary skill in the art would not expect that the presently claimed composite microsphere would solve the known problems associated with insulin instability.

Additionally, even if one of skill in the art were to somehow encapsulate the zinc-insulin complex within the aqueous hydroxyethylated starch, as in the present invention, the resulting delivery vehicle would not be the same as the presently claimed invention. As is taught by Filvaroff et al., not only does the zinc-insulin complex extend the half-life of insulin in the human body, it also acts as a mechanism for controlled release of the insulin. The presently claimed invention delivers the drug in a much different fashion. The pure insulin releases from the PLGA and the acHES composite as the composite hydrates and the insulin permeates the fluid filled pores of the acHES capsule and the PLGA coating. This release continues as the acHES and PLGA biodegrade. This mechanism is, in itself, a mechanism for controlled release of the insulin. If one of skill in the art were to incorporate the zinc-insulin complex into the microsphere, the result would be much different delivery vehicle than the present invention because the zinc-insulin complex controls both the release from the PLGA as the capsule is degraded and the absorption of the insulin into the body as the zinc-insulin complex is broken down. The resulting change to the release profile as compared to the presently claimed invention is a material change to the invention, and is therefore excluded from the claims which indicate that the composite microsphere consists essentially of PLGA, acHES, and insulin (or any of the other listed biologically active compounds).

For all of the above reasons, and for the reasons of record, the presently claimed invention is not rendered obvious by the combined disclosures of Woo et

al. and Filvaroff et al. Accordingly, the applicants respectfully request that the rejection be withdrawn.

Conclusion

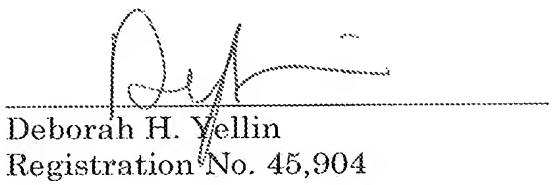
In view of the foregoing, the application is respectfully submitted to be in condition for allowance, and prompt, favorable action thereon is earnestly solicited.

If there are any questions regarding this response or the application in general, a telephone call to the undersigned would be appreciated since this should expedite the prosecution of the application for all concerned.

If necessary to effect a timely response, this paper should be considered as a petition for an Extension of Time sufficient to effect a timely response, and please charge any deficiency in fees or credit any overpayments to Deposit Account No. 05-1323, Docket No. 104072.B870248.

Respectfully submitted,

June 23, 2011



Deborah H. Yellin
Registration No. 45,904

CROWELL & MORING LLP
Intellectual Property Group
P.O. Box 14300
Washington, DC 20044-4300
Telephone No.: (202) 624-2500
Facsimile No.: (202) 628-8844
DHY/SML